IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA

Alexandria Division

HALOZYME, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 1:16-cv-1580
	)	
ANDREI IANCU,	)	
	)	
Defendant.	)	

MEMORANDUM OPINION

THIS MATTER comes before the Court on Plaintiff Halozyme, Inc.'s ("Halozyme") Complaint pursuant to 35 U.S.C. § 145, seeking reversal of a patent rejection decision issued by the United States Patent and Trademark Office ("USPTO").

I. Background

Halozyme brought this action pursuant to 35 U.S.C. § 145, challenging a final decision issued by the USPTO's Patent Trial and Appeal Board (the "Board") which affirmed the rejections of claims in U.S. Patent Application 11/238,171 ("the '171 application"). The claims were rejected on four independent grounds:

- unpatentable under obviousness-type double pantenting ("ODP") over claims 9 and 10 of U.S. Patent No. 7,767,429 ("the '429 patent") in view of the U.S.

Patent No. 5,766,897 ("Braxton") and U.S. Patent No. 6,552,170 ("Thompson");

- unpatentable under ODP over claims 4 and 5 of U.S. Patent No. 7,846,431 ("the '431 patent") in view of Braxton and Thompson;

- unpatentable under ODP over claims 5 and 6 of U.S. Patent No. 7,829,081 ("the '081 patent") in view of Braxton and Thompson; and

- obvious under 35 U.S.C. § 103(a) over WO 2004/078140 ("Bookbinder"), Braxton, and Thompson.

Halozyme was informed by the Patent Examiner during prosecution of the patent that timely-filed terminal disclaimers may be used to overcome obviousness-type double patenting rejections, but Halozyme chose not to file a terminal disclaimer to overcome any of the ODP rejections.

Halozyme is the assignee of the '171 application. The application was filed in September 2005, and is a continuation-in-part application of U.S. Patent Application No. 11/065,716 ("the '716 application"), which was filed in February 2005.

Halozyme filed its complaint in this Court on December 19, 2016, alleging that the Board erred in affirming the four rejections made by the Examiner. Halozyme amended its complaint on July 3, 2017, removing its request for judicial review of some of the claims at issue in the action, and adding an allegation that the USPTO erred by considering Bookbinder to be prior art. On August 17, 2017, Halozyme amended its complaint again, leaving only claims 295-298, 300, and 303 at issue in

this action. This Court began a bench trial on November 13, 2017, which continued until November 15, 2017.

II. Findings of Fact

Based on the evidence adduced at trial, the Court makes the following findings of fact.

A. The Relevant Technology

A protein consists of a sequence of amino acids that fold onto each other to create three-dimensional structures. As a result of the folding, some amino acids are buried and not accessible, while others are positioned along the outside of the folded structure and are accessible to the environment surrounding the protein.

There are 20 amino acids. Four of these amino acids are lysine, cysteine, arginine, and histidine, which are referenced throughout. The first amino acid of a protein is called the N-terminus.

The relationship between the various terms used throughout to describe the compounds at issue, from the broadest to narrowest, can be illustrated as follows: Glycosaminoglycanase enzymes (broadest term); Soluble neutral-active hyaluronidase Glycoprotein = sHASEGPs; Human soluble neutral-active hyaluronidase Glycoproteins = human sHASEGPs; PH-20 Hyaluronidase Glycoproteins = rHuPH20s; PEGylated rHuPH20s; PEGPH20 (Halozyme's product; narrowest term).

B. Person of Ordinary Skill in the Art

At the time of the '171 application, protein modification was an interdisciplinary field. The Court finds that a person of ordinary skill in the art would have a Ph.D. in chemistry, biochemistry, biology, or engineering, and have about two years of experience working in the field. The USPTO's experts, Dr. Zhaohui Sunny Zhou and Dr. Laird Forrest, each meet or exceed the definition of a person of ordinary skill in the art. Thus each are in a position to render an opinion as to what a skilled artisan would have thought and understood regarding the issues relevant to this case.

By 2003, it was recognized that using proteins for therapeutic purposes had several limitations. Specifically, when administered to the human body, they may exhibit a short half-life, a propensity to generate neutralizing antibodies, and proteolysis (cleavage of protein by enzymes). It was also well known by the early 2000s that attaching polyethylene glycol ("PEG") to a protein was a potential solution to overcome these problems. PEG has very low toxicity, excellent solubility in aqueous solutions, and extremely low immunogenicity and antigenicity. PEGylation was known to potentially decrease protein activity, but that decrease was generally offset by an increased half-life.

It was therefore well known that PEGylation generally extends the half-life and improves the biological activity of a protein. Braxton stated that PEGylation is the "most promising" approach to solve the problems of short half-life and immunogenicity. Thompson explained that PEGylation can "overcome obstacles encountered in the clinical use of biologically active molecules," including their short half-life in the blood stream or solubility and aggregation problems. By 2003, PEGylation was the established method of choice for improving the therapeutic use of proteins for pharmacological purposes.

PEGylation involves the formation of a covalent bond between PEG molecules and a protein. It was well known how to attach PEGs to proteins by 2003. In fact, there were two "main methods" to do so in the early 2000s. The most popular approach was to randomly attach PEGS to an amine group, which could be found on lysine amino acids and the N-terminus of the protein, among other places on the protein.

By the early 2000s, there were plenty of examples of attaching PEGs to amine groups, and in fact the majority of PEGylated drugs at that time were PEGylated at an amine group. Dr. Zhou testified that lysine PEGylation was the most common method because lysines are one of the more common amino acids and tend to be found on the protein surface, making them accessible and less likely to disrupt the function or structure

of the protein. Dr. Zhou also testified that in 2003 there were high quality commercial reagents available to conjugate PEGs to lysines, and there were methods to optimize conjugation for lysines. By 2003, attaching PEGS to amine groups via a succinimidyl (or "NHS") ester reagent was well known in the art.

The second possible approach for attaching PEGs to proteins was targeting attachment to cysteine amino acids. If a protein naturally includes a cysteine, it can by PEGylated. If it does not, a person skilled in the art can engineer a cysteine into the polypeptide, and then modify that cysteine with PEG. This approach was generally not feasible, however, if the cysteines were located in regions important to the function of the protein.

In the early 2000s, the biopharmaceutical company Nektar sold a selection of PEGylation reagents. The most popular PEG reagents Nektar sold for lysine attachment were the NHS active esters. Nektar's catalog also included instructions on how to use those reagents. Nektar teaches that multiple PEGs can be attached to a protein at multiple lysines. For lysine active PEGs, Nektar instructs that "several PEGs can be attached to a protein at pH 8-9.5 at room temperature, and within 30 minutes, if equal molar amounts of PEG (MW 5,000 Da) and protein are mixed." The Nektar catalog also explains how to optimize, stating that "[a]nalysis of several reactions with varying

ratios of PEG/protein and with varying pH will quickly provide information sufficient to design optimal conditions for desired degrees of PEGylation."

Nektar routinely partnered with other companies to develop PEGylated proteins, including identification of an appropriate PEGylation reagent, creation of a scalable process, and analytical characterization of the final modified product. The Nektar catalog reported success in PEGylating proteins, stating that their technology and development expertise have been the "driving" force behind more than five products on the market and ten products in clinical development. The catalog also included a "case study" where Nektar partnered with InterMune, reporting that "Nektar scientists created an optimized PEGylated molecule, produced a scalable process, and provided analytical characterization of the final product within three months." Dr. Zhou testified at trial that "figuring out the degrees of PEGylation" in this case study necessarily took "less than three months to do" because it is only part of the first step (creating an "optimized PEGylated molecule") of the three steps that Nektar performed.

The fact that PEGylation generally increases half-life but decreases activity would motivate a skilled artisan to figure out the optimal degree of PEGylation. The degree of PEGylation is perhaps the most important parameter, because a change in

structure can affect function; therefore, a person of ordinary skill in the art would be motivated to optimize the degree of PEGylation by routine optimization methods.

By the early 2000s, a skill artisan knew how to attach PEGs to a protein, and a person of ordinary skill in the art would know how to control how many PEGs were attached and how to test to see how many PEGs were attached. A skilled artisan could optimize PEGylation by creating a PEGylated protein and then test it for activity and longevity. The degrees of PEGylation could then be varied until the result met the desired criteria for optimization. It was also generally known how to evaluate the pharmacokinetics of a protein, with multiple examples present in the literature.

Assays to measure hyaluronidase were also known in the art. Bookbinder and the '716 application describe the same prior art assays dating back to the 1940s. They include assays measuring loss of turbidity, loss of viscosity, and the generation of new reducing N-acetylamino groups, and a substrate gel zymography assay. Other assays were also known.

Although Dr. Flamion testified that "you probably would need to adjust and improve on the existing assays," Dr. Zhou explained that if any assays needed to be adjusted, a person of ordinary skill in the art would know how to do so. Further, when you have multiple assays available, there is a "very high

success rate to adopt a new assay." Thus a person of ordinary skill in the art would be motivated to optimize the degree of PEGylation, would know how to do so, and would expect to be successful in doing so.

By the early 2000s, a number of PEGylated proteins had been approved by the FDA. The majority of these attached the PEGs at lysines and the N-terminal amino acid of the protein. By 2005, the amino acid sequence of human PH20 was known. At this time a skilled artisan would know that the cysteines in hyaluronidase involve some disulfide bonds, and because of this would not be a good target for PEGylation. This would motivate a skilled artisan to look to lysine PEGylation instead.

A skilled artisan in the early 2000s would also know how to formulate protein compositions for systemic use, including PEGylated compositions, and was motivated to do so. There was no testimony adduced at trial to suggest that any special ingredients were required to formulate a composition of hyaluronidase for systemic use, or that PEGylated hyaluronidase requires any special formulations for systemic administration.

C. The '171 Application

The '171 application lists six people as its inventors: Louis H. Bookbinder, Anirban Kundu, Gregory I. Frost, Michael F. Haller, Gilbert A. Keller, and Tyler M. Dylan. Halozyme filed a

petition with the USPTO during the prosecution of the application to remove Haller, Keller, and Dylan as inventors.

The '171 application is directed to glycosaminoglycanase enzymes; specifically, to "Neutral-Active, Soluble Hyaluronidase Glycoproteins" (or "sHASEGPs"). The application discloses "the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as rHuPH20s)," and discloses that "[c]hemical modifications of a SHASEGP" with "polymers such as polyethylene glycol and dextran" are able to "shield" sHASEGPs from "removal from circulation and the immune system as well as glycosylation receptors for mannose and asialoglycoprotein," and thus, "prolong the [] half-life" of the sHASEGP. The application also discloses modifications using polyethylene glycol to further prolong half-life and specifically discloses a modification accomplished by lysine PEGylation. One example in the '171 application, Example 21-A, discloses using succinimidyl PEGs to form PEGylated PH20 modified with "about three to six" PEG molecules, which were purified to yield compositions having "specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity." Example 21-A also discloses that a PEGylated PH20 modified with "about three to six" PEG molecules was observed to have a significantly longer serum half-life in comparison to unPEGylated PH20 when tested on mice. PEGylated

PH20 modified with "about three to six" PEG molecules also had a significantly greater effectiveness in a rat stroke model.

The '171 application discloses and provides examples of sHASEGPs being delivered systemically, and lists examples of pharmaceutically acceptable carriers, vehicles, and agents. The '171 application further discloses a variety of assays for testing hyaluronidase activity. The application discloses SEQ ID NO: 1, which it identifies as the polypeptide sequence of human hyaluronidase, and SEQ ID NO: 4, which corresponds to amino acids 36-483 of SEQ ID NO: 1. The application discloses that insulin can be used as an agent and combined with sHASEGPs by co-formulation or co-administration, and also contemplates administering hyaluronidase with a cosmetic agent.

D. The Claims of the '171 Application

The rejected claims at issue in this case are claims 295-98, 300, and 303. Halozyme has dropped claim 264 from the case, but each of the other rejected claims is dependent on claim 264, and therefore incorporates each limitation of claim 264. Independent claim 264 recites:

> A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein: the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule; the hyaluronidase polypeptide is a human-derived hyaluronidase; and the composition is formulated for systemic administration.

None of the rejected claims recite a hyaluronidase assay, a specific activity level, a specific half-life, a particular level of stability or a stabilizer, a specific therapeutic effect, or specification as to where on the hyaluronidase molecule the PEGs are to be attached.

E. The '716 Application

The '171 application is a continuation-in-part of the '716 application, which was filed in February 2005. At trial, Halozyme's expert testified that the '716 application provided written description support for the amino acid sequences of the rejected claims. Specifically, he opined that paragraph 39 of the '716 application provided written description support for the amino acid sequence of rejected claim 296. That claim recites amino acid sequences beginning at amino acid 36. The relevant portion of paragraph 39 states: "[a]mong these are polypeptides that include a sequence of amino acids that has at least 70%, 80%, 85%, 90%, 95%, or 100% sequence identity to SEQ ID No. 1 or 3."

F. Halozyme's Three Previous Patents

Halozyme already owns three U.S. patents that claim an active PEGylated truncated human hyaluronidase glycoprotein. These are U.S. Patent No. 7,767,429 ("the '429 patent"), U.S. Patent No. 7,846,431 ("the '431 patent"), and U.S. Patent No. 7,829,081 ("the '081 patent"). The claims of the '429 patent

disclose a neutral active hyaluronidase glycoprotein modified with PEG or dextran, and discloses that it may be formulated in pharmaceutical compositions. The patent discloses that sHASEGPs can be "delivered systemically by intravenous infusion." It also discloses SEQ ID No: 1 and identifies it as the polypeptide sequence of human hyaluronidase, and SEQ ID NO: 4, which corresponds to amino acids 36-483 of SEQ ID NO: 1.

The '431 patent claims a "pharmaceutical composition" comprising an active PEGylated truncated human hyaluronidase glycoprotein. The patent also includes an example (Example 21) which discloses the use of succinimidyl PEGs to form PEGylated PH20 modified with "about three to six" PEG molecules. Example 21 further discloses that a PH20 with about three to six PEGs had a significantly increased half-life over unPEGylated PH20 when tested through intravenous injection in mice. The patent also disclosed greater effectiveness of PEGylated PH20 with about three to six PEGs in a rat stroke model. Like the '429 patent, the '431 patent discloses and identifies SEQ ID NO: 1 and SEQ ID NO: 4.

The '081 patent also claims a "pharmaceutical composition" comprising an active PEGylated truncated human hyaluronidase glycoprotein. It also includes an example of using succinimidyl PEGs to form PEGylated PH20 modified with about three to six PEG molecules, and reports identical results as the '431 patent and

the '171 application. The '081 patent also discloses and identifies SEQ ID NO: 1 and SEQ ID NO: 4.

G. Bookbinder, Braxton, and Thompson

The international patent application WO 2004/078140 ("Bookbinder") was filed on March 5, 2004, and published on September 16, 2004. The patent discloses PEGylation of human hyaluronidase glycoprotein. It discloses that "[c]hemical modifications of a sHASEGP with polymers such as polyethylene glycol and dextran" can "shield sHASEGP's from removal from circulation and the immune system," resulting in increased half-life of the sHASEGP. It specifically discloses PEGylation and how it may be accomplished, and includes numerous claims to PEGylated sHASEGP.

Bookbinder discloses that sHASEGPs can be administered systemically, may be formulated into pharmaceutical compositions, and describes the pharmaceutically acceptable carriers that may be used. Bookbinder also discloses several uses for PEGylated sHASEGPs, teaches a variety of assays for testing hyaluronidase activity, and discloses SEQ ID Nos. 1 and 4.

U.S. Patent No. 5,766,897 ("Braxton") was filed April 21, 1995 and issued June 16, 1998. Braxton describes how the development of protein therapeutics was "hampered by the relatively short half-life of proteins after administration, as

well as their immunogenicity." Braxton discusses several potential solutions to these problems, but concludes that the "most promising" approach is PEGylation, which results in longer half-life and reduced immunogenicity while maintaining biological activity.

Braxton states that PEGylation typically involves an activated PEG reacting with lysine residues on the protein's surface. It teaches that if all of the lysines in the protein are modified, activity is generally lost, whereas partial PEGylation of a protein usually results in "only about 50% loss of activity and greatly increased serum half-life, so that the overall effective dose of the protein is lower." Braxton also states, however, that partial modification of this type may have some undesirable effects on the protein that can render the use of PEGylated proteins economically impractical. The specific invention in Braxton instead involves cysteine PEGylation.

U.S. Patent No. 6,552,170 ("Thompson") was filed June 14, 1994 and issued April 22, 2003. The patent is generally directed to PEGylation of polypeptides with various reagents. It states that PEGylation is used "to overcome obstacles encountered in the clinical use of biologically active molecules," particularly short half-life problems and immunogenic reactions. Thompson reveals that lysine PEGylation was the most common approach, but that this method has some drawbacks.

H. The Board's Decision

The Board's decision concluded that all of the pending claims were unpatentable on the ground of obviousness-type double patenting over each of Halozyme's earlier issued patents (the '429, '431, and '081 patents), and on the ground of obviousness over the prior art. The Board adopted the Examiner's findings and analysis concerning the scope and content of the prior art.

The Examiner had found that "[t]here is a large volume of art dedicated to the PEGylation of proteins/enzymes for use in pharmaceutical compositions." He found that this was already "an established methodology in the art" at the time of the invention, used to increase half-life and decrease immunogenicity. The Examiner referred to both Braxton and Thompson as examples of the state of the art at the time of the invention, and found that they both "provide one of ordinary skill in the art with motivation to optimize the number of PEG moieties for each protein." The Examiner found that Braxton and Thompson teach that PEGylation of proteins was routine. The Examiner also found that in view of Braxton and Thompson, it would have been obvious to a person of ordinary skill in the art to optimize the number of PEGs to achieve the longest possible half-life while maintaining maximum activity.

The Examiner rejected all of the pending claims on ODP grounds over claims 9 and 10 of the '429 patent. Halozyme chose not to file a terminal disclaimer to overcome this rejection, and so the rejection was maintained. When Halozyme appealed this rejection to the Board, it argued that its claims were not obvious over claims 9 and 10 because those claims do not recite a hyaluronidase with three to six PEGs. However, the Board agreed with the Examiner that the determination of the optimum number of PEGs per hyaluronidase molecule would be a matter of routine optimization for a skilled artisan rendered obvious by Braxton and Thompson, and thus upheld the rejection.

Similarly, the Examiner also rejected all of the pending claims on ODP grounds over claims 4 and 5 of the '431 patent. On appeal to the Board, Halozyme again argued that these claims did not recite a hyaluronidase modified with three to six PEGs, but the Board agreed with the Examiner that this was simply a matter of routine optimization that would be obvious to a skilled artisan.

The Examiner also rejected the pending claims on ODP grounds over claims 5 and 6 of the '081 patent, once again finding that the optimization of the number of PEGs would be obvious in light of Braxton and Thompson, and the Board agreed on appeal.

Finally, the Examiner also rejected the pending claims as obvious over Bookbinder, Braxton, and Thompson. The filing date of each of these references pre-dates the September 2005 filing date of the '171 application, as well as the filing date of the '716 application. The Examiner found that Bookbinder discloses an active truncated human hyaluronidase glycoprotein modified with a PEG polymer, and teaches PEGylation to increase half-life and reduce immunogenicity. The Examiner noted that Bookbinder does not specifically teach attachment of about three to six PEGs, but that there was a "large volume of art dedicated to the PEGylation of proteins/enzymes for use in pharmaceutical compositions" at the time of the invention, and selected Braxton and Thompson to exemplify this. The Examiner found that only routine optimization and experimentation was necessary to find the optimal number of PEGs.

The Board affirmed the rejection on appeal. The Board agreed with the Examiner's findings regarding Bookbinder, found that Bookbinder teaches all of the claim limitations except "about three to six [PEGs]," and was not persuaded by Halozyme's argument that it would not have been obvious to determine that three to six PEGs was the optimal amount to increase half-life while maintaining activity. The Board found that it would have been a matter of routine optimization for a person of ordinary skill in the art to determine a range of three to six PEGs, and

that a person of ordinary skill in the art would be motivated to do so.

I. Halozyme's Evidence of Secondary Considerations

At trial, Halozyme presented evidence of secondary considerations to combat the obviousness rejections. This included evidence of unexpected results, commercial success, industry praise, and long-felt but unmet need.

Halozyme offered the testimony of Dr. Flamion at trial, who stated that Example 21-A in the '171 application supported a finding that Halozyme's rejected claims demonstrate unexpected results. That example reports that a PEGylated hyaluronidase has an increased serum half-life in mice and increased survival in a rat stroke model, as compared with unmodified hyaluronidase. Dr. Flamion stated that this improvement was due to the "specific PEGylation of three to six" moieties in contrast to "the non-PEGylated" protein. Notably, the Board considered Halozyme's assertion that Example 21-A provided evidence of unexpected results, but found this to be unpersuasive in light of the fact that Halozyme's previous patents and the prior art already disclosed PEGylated hyaluronidase and taught that PEGylating could increase half-life.

To demonstrate commercial success, Halozyme presented evidence of a May 2017 stock sale that generated $135 million in "general investment" funds for Halozyme. Potential investors

participating in that stock sale were presented with a slide titled "Why Invest in Halozyme" that highlighted two products: PEGPH20 and ENHANZE. Of the two, ENHANZE is Halozyme's only revenue-generating product, as PEGPH20 lacks FDA approval and is not on sale. There is no commercial product embodying Halozyme's pending claims.

PEGPH20 is Halozyme's PEGylated hyaluronidase drug product. It is expected to be effective only in a subset of cancer patients: those with solid tumors that accumulate high hyaluronan levels. PEGPH20 has a weighted average of between three to six PEGs per hyaluronidase molecule, but the full range is much broader, from two to eight or more.

A February 28, 2017 Prospectus Supplement from Halozyme stated that investment proceeds in Halozyme's common stock was intended to be used to fund the development of PEGPH20, but also to be used for "other general corporate purposes." The Prospectus Supplement further indicated that "management will have broad discretion as to the application of net proceeds and [can] use them for purposes other than those contemplated at the time of . . . offering."

The USPTO presented the testimony of Ivan Hofmann, a managing director of Gleason IP and leader of its intellectual property practice, as an expert in pharmaceutical economics. Mr. Hofmann testified that it was his opinion that Halozyme's

evidence of alleged commercial success did not provide any objective indicia of nonobviousness.

Halozyme offered evidence of industry praise through the testimony of Dr. Flamion, who supported his testimony by reference to a paper published by the Cancer Cell journal describing the results of a mouse study on PEGylated PH20, and Halozyme's clinical research proposals and agreements. Dr. Flamion also testified that the claimed invention met a long-felt but unmet need through its potential applications in cancer treatment.

III. Conclusions of Law

35 U.S.C. § 145 provides a civil action remedy for a patent applicant whose patent application has been rejected by the Board. In a § 145 action, the plaintiff bears the burden of establishing error by the Board. See Fregeau v. Mossinghoff, 776 F.2d 1034, 1038 (Fed. Cir. 1985). A § 145 action is a "hybrid" action, partly an appeal from an administrative body, and partly a new evidentiary proceeding. Hyatt v. Kappos, 625 F.3d 1320, 1322 (Fed. Cir. 2010) ("Hyatt I"), aff'd, Kappos v. Hyatt, 132 S. Ct. 1690 (2012) ("Hyatt II"). Any new evidence submitted to the court on a disputed factual question is considered *de novo*, Hyatt II, 132 S. Ct. at 1700, while factual findings made by the Board which are untouched by new evidence presented to the court

are reviewed under the substantial evidence standard mandated by the Administrative Procedure Act, Hyatt I, 625 F.3d at 1336.

However, "the applicant does not start over to prosecute his application before the district court unfettered by what happened in the PTO." Fregeau, 776 F.2d at 1037-38. Instead, the court's factual findings must take into account "both the new evidence and the administrative record before the PTO," by "assess[ing] the credibility of new witnesses and other evidence, determin[ing] how the new evidence comports with the existing administrative record, and decid[ing] what weight the new evidence deserves." Hyatt II, 132 S. Ct. at 1700, 1701.

A. Rejected Claims are Unpatentable on Obviousness-Type Double Patenting Grounds over Halozyme's '429, '431, and '081 Patents

In light of the evidence adduced at trial, the Court concludes that Halozyme's rejected claims are unpatentable on ODP grounds over each of Halozyme's '429, '431, and '081 patents.

Obviousness-type double patenting ("ODP") is a judicially created doctrine that prohibits an individual from obtaining more than one patent on the same invention, thus preventing a patentee from extending his or her exclusive rights beyond the expected patent term. See Abbvie Inc. v. Mathilda and Terence Kennedy Inst., 764 F.3d 1366, 1372 (Fed. Cir. 2014). A determination of double patenting is ultimately a question of

law. Georgia-Pacific Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1326 (Fed. Cir. 1999).

An ODP analysis consists of two steps. First, the claims in the earlier referenced patent and in the later patent (or application) are construed and the differences (if any) are determined. See Ely Lilly and Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). Next, the differences are examined to ascertain whether the later claims are patentably distinct from the earlier reference claims. Id. A later claim is not patentably distinct from an earlier claim if the later claim is obvious over, or anticipated by, the earlier claim. Pfizer, Inc. v. Teva Pharms. USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008).

A double patenting rejection is particularly appropriate where a patentee has a broad claim and then applies for a claim to a narrow embodiment. See In re Schneller, 397 F.2d 350, 355 (C.C.P.A. 1968); In re Metroprolol Succinate Patent Litigation, 494 F.3d 1011, 1018 (Fed. Cir. 2007).

All of Halozyme's rejected claims are unpatentable on ODP grounds over claims 9 and 10 of Halozyme's '429 patent. The claims of Halozyme's '171 application are nearly identical to claims 9 and 10 of Halozyme's '429 patent. Both sets of claims recite a PEGylated hyaluronidase that is active at neutral pH, truncated regions of SEQ ID NO: 1, and at least one sugar moiety covalently attached to an asparagine (N) residue.

Halozyme asserts that the rejected claims are patentably distinct from claims 9 and 10 of the '429 patent because the rejected claims recite a selection of "about three to six PEG moieties." However, this is not a patentable distinction, because the '429 patent allowed for modification with any number of PEGs. "Selecting a narrow range from within a somewhat broader range disclosed in a prior art reference" is *prima facie* obvious under 35 U.S.C. § 103(a) "because the 'normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum . . . .'" In re Peterson, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003). A person of ordinary skill in the art would be motivated to find the optimal degree of PEGylation, because adding PEGs to a protein is a balancing act between increasing half-life and decreasing activity of the protein.

Additionally, the Braxton and Thompson prior art also provide a motivation to optimize the degree of PEGylation. Braxton teaches that a "full modification" will typically result in activity being lost. Braxton teaches that a one should instead "[g]o for a partial modification," and "[f]or partial [modification], you have to figure out where the partial is." Thompson teaches that the molecular weights of PEGs can vary and the rate of clearance is related to the molecular weight, thus

providing further motivation to optimize the degree of PEGylation.

A person of ordinary skill in the art would know how to optimize the number of PEGs and would have a reasonable expectation of success doing so. Thus, the Board correctly found and the evidence presented in this case establishes that one skilled in the art would view the selection of between three and six PEG moieties to be a matter of routine optimization generally required by the PEGylation process itself.

Similarly, the rejected claims are also unpatentable on ODP grounds over claims 4 and 5 of Halozyme's '431 patent. Both sets of claims recite a "pharmaceutical composition," a PEGylated hyaluronidase that is active and neutral pH, truncated regions of SEQ ID NO: 1, and at least one sugar moiety covalently attached to an asparagine (N) residue. The term "about three to six PEG moieties" in the '171 application claims is not a patentable distinction from claims 4 and 5 of the '431 patent for the same reasons that the term is not a patentable distinction from claims 9 and 10 of the '429 patent. Additionally, the '431 patent's sole example of a PEGylated human hyaluronidase discloses that a human hyaluronidase PEGylated with "about three to six" PEGs exhibited activity in experimentation. Thus it would be obvious to select "about three

to six" PEGs when practicing the claimed active PEG-modified hyaluronidase of the '431 patent.

The rejected claims are also unpatentable on ODP grounds over claims 5 and 6 of the '081 patent, for all of the same reasons discussed with regard to the '431 patent. The claims are almost identical, and the term "about three to six PEG moieties" is not a patentable distinction for all of the same reasons discussed *supra*.

B. Rejected Claims are Unpatentable as Obvious over Bookbinder, Braxton, and Thompson

The Court further concludes that Halozyme's rejected claims are unpatentable as obvious over the prior art of Bookbinder, Braxton, and Thompson.

Section 103(a) of the Patent Act describes the patentability requirement that has come to be known as "obviousness" as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. § 103(a).

In determining obviousness, courts must consider factors such as the scope and content of the prior art, the differences between the prior art and the claims at issue, the level of

ordinary skill in the art, and secondary considerations including, but not limited to, commercial success, failure of others, long-felt yet unsolved need, and copying. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406-07 (2007) (quoting Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966)). The test for obviousness, stated simply, is "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413 (C.C.P.A. 1981). Whether a person of ordinary skill in the art would have been motivated to modify or combine references is a question of fact. In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000). Additionally, as noted previously, the Federal Circuit has held that a selection of a narrow range from within a broader range disclosed in a prior art is *prima facie* obvious. Peterson, 315 F.3d at 1329-30.

A finding that a prior art reference "teaches away" from the claimed invention is a significant factor weighing toward a determination of nonobviousness, but it is not dispositive. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006). Further, the "mere disclosure of alternative designs does not teach away," but rather the prior art must disclose that the method used in the claimed invention "should not" or "cannot" be used. In re Mouttet, 686 F.3d 1322, 1334 (Fed. Cir. 2012).

The Examiner and the Board both found that Bookbinder teaches every element of the rejected claims except for the specification of "about three to six" PEGs. This Court agrees with that finding. This Court also agrees with the Examiner and the Board that there was "a large volume of art dedicated to the PEGylation of proteins/enzymes for use in pharmaceutical compositions," and that Braxton and Thompson "exemplify the state of the art at the time of the invention." A skilled artisan would have been motivated to experiment and adjust the degree of PEGylation to achieve the optimal balance between increased half-life and decreased protein activity. Braxton and Thompson also provide a motivation to find the optimal degree of PEGylation. A skilled artisan would know how to optimize the degree of PEGylation, would have had a reasonable expectation of success in doing so, and it would be routine to do so. Thus, the Court holds that one skilled in the art would view the selection of between three and six PEG moieties to be a matter of routine optimization.

C. Halozyme's Arguments Regarding ODP Rejections Fail

At trial, Halozyme presented new arguments to contradict the Board's ODP rejections which were not presented to the Board. This Court holds that none of these arguments have merit.

First, regarding the '429 patent, Halozyme argues that the term "pharmaceutical composition," appearing in the preamble of

claim 264, is a patentable distinction from claims 9 and 10 of the '429 patent. In the first instance, this argument fails because the term "pharmaceutical composition" is not a limitation of the rejected claims, but merely a statement of the purpose or intended use of the invention. See Symantec Corp. v. Computer Associates Int'l, Inc., 522 F.3d 1279, 1288 (Fed. Cir. 2008) ("A preamble is not limiting, however, 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.'") (quoting Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002)).

Moreover, even assuming that the term "pharmaceutical composition" is a claim limitation, it is not a patentable distinction from claims 9 and 10 of the '429 patent. Halozyme based its argument on its expert's testimony that the "idea to develop a pharmaceutical composition is completely different from the idea of preparing an enzyme that is not soluble and active." However, claims 9 and 10 of the '429 patent recite a hyaluronidase glycoprotein that is both "soluble" and "active," just like the rejected claims. Furthermore, using a known protein pharmaceutical composition formulated for systemic administration of the PEG-modified hyaluronidase of claims 9 and 10 of the '429 patent would have been obvious to one of ordinary skill in the art.

Second, Halozyme argues that the term "formulated for systemic administration" in the rejected claims is a patentable distinction from claims 9 and 10 of the '429 patent. Once again, this argument fails, because it would have been obvious for a skilled artisan to use a known protein pharmaceutical composition formulated for systemic administration based on the claims of the '429 patent.

Third, regarding the '431 patent, Halozyme argues that the term "formulated for systemic administration" is a patentable distinction from claims 4 and 5 of the '431 patent. This is based on Dr. Flamion's testimony at trial that claim 5 "is a composition that is designed for local administration." Dr. Flamion further testified that a composition of hyaluronidase insulin would not be injected in intravenous form (i.e., systemic administration), but that it would "need to be injected locally in order to improve the diffusion of insulin to allow its access to the bloodstream and so on." However, a subcutaneous injection designed to enter the bloodstream, such as insulin, is available systemically once it reaches the bloodstream. Halozyme's argument is based on an overly narrow definition of "formulated for systemic administration" and therefore fails.

Fourth, Halozyme argues that the term "insulin" in the '431 patent's claims is a patentable distinction. This argument is

unavailing, however, because claim 264 of the '171 application recites a "pharmaceutical composition *comprising* . . . ," and therefore it is broad enough to cover compositions comprising a PEGylated hyaluronidase and another element not specifically recited. Furthermore, the '171 application specifically contemplates the use of insulin as an agent that can be combined with SHASEGPs by co-formulation or co-administration.

Fifth, regarding the '081 patent, Halozyme argues that the term "formulated for systemic administration" is a patentable distinction from claims 5 and 6 of the '081 patent, which relates to a cosmetic agent. However, at trial, Dr. Zhou provided examples of cosmetic agents administered systemically for certain skin conditions, and the '171 application itself confirms that even "topical" mixtures can be administered systemically.

Sixth, Halozyme argues that the term "cosmetic agent" in claims 5 and 6 of the '081 patent is a patentable distinction. As discussed with regard to the term "insulin" in the '431 patent, however, the term "comprising" in claim 264 of the '171 application is broad enough to include other elements not specifically recited. Additionally, the '171 application contemplates administrating hyaluronidase with a cosmetic agent.

D. Halozyme's Arguments Regarding Obviousness Rejection Fail

Halozyme also raised several new arguments regarding the obviousness rejection that were not presented to the Board. The Court holds that each of these arguments fail for the reasons discussed below.

First, Halozyme argues that the Board's findings of fact were not supported by the evidence. However, many of the Board's findings of fact are direct quotations from prior art references. The Board's finding of fact 5, finding that "Braxton teaches PEGylation of proteins that are suitable for therapeutic uses," is not a direct quotation, but it is supported by Braxton's disclosure. Thus, the Court holds that each of the Board's findings of fact is supported by substantial evidence.

Halozyme next argues that a person of ordinary skill in the art would not have been motivated to PEGylate hyaluronidase. However, the Bookbinder reference teaches PEGylation of hyaluronidase. The Examiner and the Board relied on this reference. It is thus irrelevant for determining obviousness to question whether a person of ordinary skill in the art would be motivated to PEGylate hyaluronidase; instead, the question is whether they would be motivated to optimize the PEGylation of a hyaluronidase that has already been PEGylated. The fact that Bookbinder also teaches alternative methods is irrelevant

because a prior art reference is applicable for all that it teaches or suggests to a person of ordinary skill in the art. See In re Inland Steel, 265 F.3d 1354, 1361 (Fed. Cir. 2001).

Halozyme also argues that a person of ordinary skill in the art would not have had a reasonable expectation of success PEGylating hyaluronidase. This is irrelevant for the same reason discussed previously: the Bookbinder reference includes extensive disclosures regarding PEGylation, and even includes claims to a PEGylated hyaluronidase glycoprotein. Halozyme's evidence on this point does not establish that a person of ordinary skill in the art would not have a reasonable expectation of success based on the prior art.

Halozyme asserts that the prior art references of Braxton and Thompson would discourage an artisan from lysine PEGylation of hyaluronidase. But this argument once again ignores the fact that Bookbinder already discloses a PEGylated hyaluronidase and teaches lysine PEGylation, which is the same approach used in the '171 application. Thus, this argument also fails.

Halozyme argues next that Bookbinder focuses on a composition formulated for local administration, and therefore a pharmaceutical composition formulated for systemic activity is not obvious in light of Bookbinder. However, there is no dispute that Bookbinder does disclose systemic administration, and a prior art reference is applicable for all that it teaches or

suggests to a person of ordinary skill in the art. In re Inland Steel, 265 F.3d at 1361.

Halozyme's final argument against Bookbinder is that the reference is not prior art to the '171 application under 35 U.S.C. § 102. Halozyme makes this argument by asserting that the claims of the '171 application are entitled to an earlier priority date one year or less after the disclosure of Bookbinder. Halozyme must prove that the '171 application is entitled to the earlier priority date in order to establish that Bookbinder is not prior art. See 35 U.S.C. § 102(b)(1). The Court holds that Halozyme has failed to do so.

Halozyme argues that the '171 claims are entitled to the February 2005 priority date of an earlier application, the '716 application, which would be less than one year after Bookbinder's publication in September 2004. In order to prove this, Halozyme must meet its burden to show that the '716 application included "written description" support for the rejected claims. See 35 U.S.C. § 112; PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1305-06 (Fed. Cir. 2008). "[A] patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112." Id. at 1306. Section 112 in turn requires "written description" support. 35

U.S.C. § 112(a). To meet the written description requirement, "the prior application must indicate to a person skilled in the art that the inventor was 'in possession' of the invention as later claimed." PowerOasis, 522 F.3d at 1306. "[A] description that merely renders the invention obvious does not satisfy the requirement." Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010).

Halozyme adduced at trial through the testimony of an expert witness that the '716 application included written description support for the amino acid sequences of the rejected claims. However, the same witness testified that this description is "very broad" and "a lot broader than what is in the [rejected] claim." The description at issue does not contain specific wording explaining where to begin or end within the described amino acid sequence to match the sequences of the rejected claims. Thus, Halozyme failed to demonstrate that the '716 application would direct a skilled artisan to the later claimed invention, and therefore Halozyme has not demonstrated that the '716 application provides written description support for the rejected claims.

E. Halozyme's Arguments Regarding Secondary Considerations Fail to Overcome Unpatentability Determination

Relevant secondary considerations that a court may consider in making an obviousness determination include commercial

success, industry praise, long-felt but unsolved needs, failure of others, and unexpected results. Halozyme has failed to present persuasive evidence of secondary considerations sufficient to overcome the USPTO's obviousness and ODP rejections.

In order to use evidence of secondary considerations to overcome an obviousness determination, the plaintiff must first establish a nexus between the evidence and the merits of the claimed invention. In re GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995). Such a nexus may not exist where the merits of the claimed invention were "readily available in the prior art." See Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1580 (Fed. Cir. 1983). Where the *prima facie* case for obviousness is strong, even substantial evidence of secondary considerations may be inadequate to overcome a determination of obviousness. Leapfrog Enterprises, Inc. v. Fisher-Price, Inc., 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Halozyme first offers evidence of unexpected results as a secondary considerations argument. The Federal Circuit has held that "[t]o be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." Bristol-Meyers

Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014).

As has already been discussed, PEGylated, neutral active, soluble human hyaluronidase was already disclosed in the prior art as well as in Halozyme's issued patents. Thus Halozyme must show nexus by establishing that any unexpected results stem from a distinguishing limitation of the '171 claims. Halozyme asserts that the distinguishing limitation is the attachment of three to six PEGs. However, the data offered by Halozyme to show unexpected results only compares half-life and activity between an unmodified hyaluronidase and one that is modified with three to six PEGs. Since the prior art already discloses PEGylated hyaluronidase with increased half-life and biological activity, Halozyme has failed to show unexpected results as compared to the closest prior art and therefore failed to show the required nexus. See In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Halozyme also offered evidence of commercial success of its product PEGPH20 as a secondary consideration. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in

the art." Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005).

In the first instance, Halozyme has again failed to prove a nexus between the alleged commercial success of PEGPH20 and the '171 application. Even assuming that PEGPH20 is covered by the '171 application claims, it was adduced at trial that PEGPH20 may be effective in only a subset of patients as it "is focused on treating solid tumors that accumulate high levels of hyaluronan" and thus any alleged commercial success it has achieved may be due to this characteristic of the product. The claimed invention, to the contrary, is not limited to treatment of such tumors.

Beyond this, even if a nexus were established, Halozyme cannot demonstrate commercial success for PEGPH20 because it has not been approved by the FDA and is not on sale. There can be no commercial success if there is no commercial product. Thus, it is impossible at this point to find objective evidence of the product's performance. The evidence Halozyme has submitted is not the kind that is typically used to establish non-obviousness, which generally includes historical data and metrics, profitability, and market share.

Halozyme's evidence of its stock sale is not persuasive, because the asserted commercial success must be due to the merits of the claimed invention itself. Halozyme approached

potential investors with only two products: PEGPH20 and ENHANZE. ENHANZE was the only product of the two generating revenue. Additionally, Halozyme's February 28, 2017 Prospectus Supplement shows that the financing generated from Halozyme's stock sale was not limited to funding PEGPH20, but rather could be used for "general corporate purposes" and that management had broad discretion in determining the use of these proceeds. The stock sale therefore represents investment in the company, and is not objective evidence of commercial success of one particular product.

Halozyme has also asserted evidence of industry praise and recognition as a secondary consideration. Evidence of industry praise and recognition is considered relevant because industry participants, particularly competitors, are unlikely to praise an obvious advance over the known art. See Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1053 (Fed. Cir. 2016). None of the evidence presented on this point is praise from a competitor, and the Court finds that it does not constitute industry praise or recognition. The Court concludes that Halozyme's asserted evidence of industry praise and recognition is unpersuasive and insufficient to overcome the strong case for unpatentability established by the USPTO.

Finally, Halozyme has also offered evidence of a long-felt but unsolved need resolved by the claimed invention. This sort

of secondary consideration evidence is relevant in determining obviousness "because it is reasonable to infer the need would not have persisted had the solution been obvious." Apple, 839 F.3d at 1056. The proponent of such evidence must establish first that the long-felt need existed, and secondly that the claimed invention satisfied the need. In re Cavanaugh, 436 F.2d 491, 496 (C.C.P.A. 1971).

The evidence Halozyme submitted regarding PEGPH20's satisfaction of a long-felt need is irrelevant, because PEGPH20 is not commercially available to meet any such need, and thus Halozyme has not demonstrated that the need has been met by the claimed invention.

For the aforementioned reasons, this Court concludes that Halozyme has not demonstrated that the USPTO erred in rejecting the claims at issue, and therefore Halozyme's requested relief shall be denied. An appropriate order shall issue.

Claude M. Hilton

CLAUDE M. HILTON
UNITED STATES DISTRICT JUDGE

Alexandria, Virginia
July 31, 2018